Blood vessel mapping reveals four new 'ZIP codes'

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A research team led by scientists from The University of Texas MD Anderson Cancer Center have discovered four new "ZIP codes" in their quest to map the vast blood vessel network of the human body.

The study, published online the week of Oct. 24 in the Proceedings of the National Academy of Sciences, brings science one step closer to the goal of using the vascular system to personalize cancer therapy, as well as fight obesity, heart disease and other disorders. Researchers also found that some addresses are shared in vasculature across the board instead of always being organ-specific.

The study is part of ongoing research to identify specific and unique addresses, or ZIP codes, within the body's vascular system and use them to develop diagnostic, imaging and therapeutic strategies. Husband-and-wife research team Wadih Arap, M.D., Ph.D., and Renata Pasqualini, Ph.D., professors at the David H. Koch Center for Applied Research of Genitourinary Cancers at MD Anderson, pioneered the concept and were senior authors of the paper.

"By identifying vascular ZIP codes, we bring medicine closer to the ultimate goal of targeted therapies," Pasqualini said.

Innovative methods help investigation

This study supports the Arap-Pasqualini lab's ongoing research to show

blood vessels are more than a uniform and ubiquitous "pipeline" that serves the circulatory system.

More than a decade ago, the group pioneered a screening technique that employs billions of viral particles, called phage, to discover, validate and use blood vessel diversity. The particles are packaged with small fragments of proteins called peptides that act as ligands. When injected into the body, they bind to specific receptors in the blood vessels and organs.

"This process is like a 'molecular mass mailing' to all addresses in the body," Arap said. "The peptides travel until they find a target and bind to it, then with our novel technology we recover and identify them. Knowing the characteristics of the peptides and where they attach can help us understand the vascular system's molecular makeup and develop therapies focusing on disease sites."

This new study was the first in which researchers evaluated the molecular repertoire of protein diversity in several patients, targeting multiple organs at once.

In three cancer patients, serial rounds of peptide collection were followed by biopsies from various tissues to determine where and how the peptides homed, which enabled the enrichment of targeting peptides for identifying ligand-receptors. After systemic delivery of a peptide library to the first patient, phage were recovered from organs, pooled and serially screened in two subsequent patients. Large-scale sequencing was then performed.

"This uncovered a new twist for the vascular map," Pasqualini said. "To this point, we had seen mainly addresses that were organ and tissue specific. Because of this synchronized method, we discovered some markers are vascular-associated at multiple sites."

Shared addresses surprise researchers

Analysis revealed four native ligand-receptors, three of which were previously unrecognized.

Two are shared among multiple tissues (integrin a4/annexin A4 and cathepsin B/apolipoprotein E3) and the other two have a restricted and specific distribution in normal tissue (prohibitin/annexin A2 in white fat tissue) or cancer (RAGE/leukocyte proteinase-3 in bone metastases).

The discovery of shared addresses especially intrigued researchers.

"No one knew about the novel aspect surrounding these particular proteins, and the fact that they can interact and come together to serve a common purpose," Pasqualini said. "There are likely to be many more."

A tissue-specific vascular-targeting system, comprising ANXA2 and prohibitin, was found as a ligand-receptor in human white adipose (fat) tissue vasculature. In earlier research, targeting of prohibitin with an apoptotic agent caused dramatic weight loss in obese rodents. The lab is applying to the Food and Drug Administration (FDA) to conduct a clinical trial for a new drug that will test this principle for weight loss in humans.

Moving the impact forward

This project establishes that large-scale study of the human vasculature can uncover many unidentified or unique molecular networks that can contribute to the treatment of many diseases.

"This endeavor and the applications of our findings are exciting," Arap said. "There are going to be many more receptors and many levels of

diversity. We've just scratched the surface."

Translational applications, such as first-in-man clinical trials, have started within MD Anderson. The FDA has granted a safe-to-proceed status for the first vascular-targeted Investigational New Drug (IND). Three other drugs are in pre-IND stage, and several others are in pre-clinical laboratory phase.

"I believe these strategies to identify therapeutic targets on the vasculature are truly innovative both from a scientific and clinical perspective," said David Cheresh, Ph.D., associate director for Translational Research at the University of California, San Diego Cancer Center and noted authority on angiogenesis and cancer metastasis. "Identifying such targets will ultimately pave the way for the next generation of smart/targeted cancer therapies."

MD Anderson and some of its researchers, including Arap and Pasqualini, have equity positions in drug-development companies Alvos Therapeutics and Ablaris Therapeutics, which are subjected to certain restrictions under institutional policy. MD Anderson manages and monitors the terms of these arrangements in accordance with its conflict-of-interest policy.

Provided by University of Texas M. D. Anderson Cancer Center